## REMARKS

The presently claimed invention features nucleic acid molecules related to nucleic acid molecules derived from a strain of *Xenorhabdus bovienii*. The nucleic acid molecules encode polypeptides that are toxic to certain nematodes. The previous claims were mis-numbered because claim 43 was missing. Thus, the highest numbered claim previously pending should have been claim 52, not claim 53. All of the pending claims have been cancelled and new claims have been added. New claims have been added starting with claim 53.

New claim 57 is supported by the specification at page 16. The additional new claims are supported by the original claims and throughout the specification. No new matter has been added.

Election/Restriction

The Examiner withdrew claims 31, 34, 37, 39-42, 50 and 52 from consideration as drawn to a non-elected invention because they include limitations to SEQ ID NO:22. New claims 54-56 and claims dependent thereon include a limitation to the amino acid sequence of SEQ ID NO:23. They also include a limitation to the amino acid sequence of SEQ ID NO:22. However, this does not mean that claims 54-56 and the claims dependent thereon are drawn to a non-elected invention. The limitation related to SEQ ID NO:22 in these claims is an additional limitation to the limitation related to SEQ ID NO:23, not an alternative limitation. Accordingly, Applicants respectfully request that claims 54-56 and claims dependent thereon be considered.

Rejections Under 35 U.S.C. §112, first paragraph (written description)

The Examiner rejected previously pending claims 43, 45-48 and 53 as allegedly failing to meet the written description requirement of 35 U.S.C. §112, first paragraph.

The Examiner, citing *Regents of the University of California v. Eli Lilly & Co.* 119 F.3d 1559 (Fed. Cir. 1997), argued that the rejected claims fail to meet the written description requirement because the specification does not teach which amino acid sequences are essential for nematicidal activity.

Newly added claim 57 is drawn to "an isolated nucleic molecule comprising a nucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 70% identical to SEQ ID NO:23, wherein the isolated nucleic acid molecule hybridizes to the portion of SEQ ID NO:52 encoding SEQ ID NO:23 at 57°C in 0.368 M $Na^+$ and 50% formamide, and wherein the polypeptide is toxic to a nematode." Thus, the nucleic acid molecules of this claim and the claims dependent thereon include limitations related to: a) the ability of the nucleic acid molecule to hybridize to a specific sequence, b) the amino acid sequence of the polypeptide encoded by the nucleic acid molecule, and c) the function of the polypeptide encoded by the nucleic acid molecule (toxicity to nematodes). The *Lilly* court has stated that the written description requirement can be met by either a disclosure of a sufficient number of species within the claimed genus or a combination of structural and functional limitations.

The Synopsis of Written Description Guidelines published by the United States Patent and Trademark Office (the "Guidelines") includes an example (Example 9) of a claim drawn to a genus of nucleic acid molecules defined by the ability to hybridize under stringent conditions to a nucleic acid molecule having a particular sequence and by the fact that the nucleic acid molecules encode a protein having a particular activity which could be assayed by a method disclosed in the application. The Guidelines state that such claims can meet the written description requirement.

When the Applicants previously noted this portion of the Guidelines, The Examiner argued that the Guidelines "do not have the force and effect of law". This is, of course, true. However, the Examiner also stated that the Guidelines are "designed to assist Office personnel in analyzing claimed subject matter for compliance with substantive law." Undoubtedly this is true, and it is true because the Guidelines were written to be in accord with the prevailing case law. Yet, the Examiner has failed to explain why the claim of Example 9 in the Guidelines meets the written description requirement, yet the present claims do not. Applicants respectfully point out that in the example in the Guidelines the specification included only one disclosed species.

Applicants also respectfully point out that Example 9 of the Guidelines explains that stringent hybridization conditions yield structurally similar molecules.

> Now turning to the genus analysis, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

In view of the forgoing, Applicants request that the rejections based on the written description requirement of 35 U.S.C. §112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph (enablement)

The Examiner rejected previously pending claims 43, 45-48 and 53 as allegedly failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph.

Present claim 53 and certain claims dependent on claim 53 are drawn to an "isolated nucleic molecule comprising a nucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 70% (85%, 90%, 95%, or 98%) identical to SEQ ID NO:22, wherein the isolated nucleic acid molecule hybridizes to the portion of SEQ ID NO:52 encoding SEQ ID NO:23 at 57°C in 0.368 M $Na^+$ and 50% formamide, wherein the polypeptide is toxic to a nematode.

Regarding the previously pending claims, the Examiner argued the number of potential peptides having at least 70% identity to a reference polypeptide the length of SEQ ID NO:23 is very large and that it would be unreasonable to screen all such polypeptides to identify those toxic to nematodes. Applicant has cancelled the previously pending claims. The present "percent identity" claims include limitations based on quite stringent hybridization conditions.

As explained in the accompanying declaration of Dr. J. A. W. Morgan (Attachment A), one of the inventors of the present application, those of ordinary skill in the art understand that DNA hybridization methods can be used to isolate genes within the same group as those in the present application (see paragraphs 8 and 9 of the declaration). As Dr. Morgan explains in his declaration, hybridization techniques have been successfully used isolated similar groups of genes even where the actual sequences are quite different (see paragraph 9).

As noted previously, the specification teaches straight forward assay for determining whether a nucleic acid molecule encodes a polypeptide that in toxic to a nematode (see pages 31-37 of the specification). Briefly, the assay entails introducing the nucleic acid into a expression vector to create an expression construct that is used to transform *E. coli* that are grown in multi-well culture dishes to generate a library of clones. *C. elegans* larvae are added to the *E. coli* cultures and the cultures are visually examined several days later to assess nematode development. Thus, the assay is well suited to high throughput library screening. Indeed, high throughput library screening was used to initially identify cHRIM5 as a clone encoding a polypeptide(s) toxic to a nematode (see page 31 of the specification).

Given the teachings of the specification, one skilled in the art could make and use the nucleic acids without undue experimentation because the specification teaches one skilled in the art how to identify nucleic acid molecules encoding biologically active polypeptides. The Court of Appeals for the Federal Circuit has identified eight factors that must be considered in determining whether undue experimentation would be required to practice a claimed invention: "(1) the quantity of experimentation necessary, (2) the amount and direction of guidance provided, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988).

With respect to the relative skill in the art, it is clear that the relative skill in art of generating variant polypeptides is very high. For example, those skilled in the art are aware of various random mutagenesis protocols can be used to create libraries of clones encoding variant polypeptides.

With respect to the guidance provided by the specification, by providing a simple, high throughput screening method, the specification provides considerable guidance in the generation and screening of variant polypeptides.

With respect to the absence or presence of working examples, the specification provides a working example of successful high throughput screening for the identification of nucleic acids encoding toxic peptides.

Regarding the breadth of the claims, it is Applicants' position that the claims are not excessively broad encompassing as they do nucleic acid molecules that both encode polypeptides having at least 70% identity to a reference sequence and hybridize under quite stringent conditions to a particular nucleic acid molecule.

With respect to predictability, although it cannot always be predicted whether a given amino acid change will alter function, it is generally understood, despite some exceptions, that certain types of variants, e.g., those involving conservative amino acid substitutions are more likely to retain function.

With respect to the amount of experimentation required, the high through-put screening methods described in the present specification are capable of testing many, many peptides very rapidly. There are two reasons for this. First, the assay itself is quite simple in so much as it involves simply exposing nematodes to a clone expressing the polypeptide of interest. Second, as of the priority date of the present application, 1999, technology was available to rapidly generate large libraries of variant polypeptides.

In view of the forgoing, Applicants respectfully request that the enablement rejections under 35 U.S.C. §112, first paragraph be withdrawn.

Enclosed is a Petition for Extension of Time with the appropriate fee along with a Request for Continued Examination ("RCE") with the appropriate fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicant | : James Alun Wynne Morgan, et al. | Art Unit | : 1635 |
| Serial No. | : 09/889,874 | Examiner | : Brian Whiteman |
| Filed | : July 23, 2001 | | |
| Title | : BIOLOGICAL CONTROL OF NEMATODES | | |

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ATTACHMENT A

Declaration by J.A.W. Morgan

# STATUTORY DECLARATION

I, James Alun Wynne Morgan, Warwick HRI, University of Warwick, Wellesbourne, Warwick CV35 9EF, declare and state that:

1. I am a project leader at Warwick HRI (formally Horticulture Research International), which position I have held since 1992.
2. I hold the degrees of Bachelor of Science (Hons, 1st Class) in Applied Biology conferred on me from the Liverpool Polytechnic (now John Moores University); and the degree Doctor of Philosophy conferred on me from Liverpool University.
3. From 1989 to 1992 I was a research fellow at the Freshwater Biological Association, Ambleside, Cumbria.
4. As well as my administrative and project leader roles, I am active in supervision of post-graduate MSc and PhD research projects.
5. I am the author or co-author of many original publications including research papers and book chapters, and I have presented papers at many international meetings.
6. In the course of my professional activities I attend national and international conferences relevant to my field of research and interest. At such conferences I meet with colleagues from the UK and abroad. This affords me the opportunity to discuss and familiarise myself with the current state of the art and new developments, both conceptual and technological.
7. I have reviewed prior to making this declaration a copy of the Patent Application (US 09/889,874) and letters and emails relating to percent similarity.
8. I believe that those skilled in the art such as myself would clearly understand that it is suitable to use DNA hybridization techniques to isolate genes that belong to a similar general group using DNA hybridization. The techniques that I and many others have used, are well documented and most experiments follow standard methods set out in classic textbooks such as that of Sambrook, Fritsch and Maniatis, Molecular cloning a laboratory manual (second edition), 1989 Cold Spring Harbor Laboratory Press, and earlier versions of this manual. In this method DNA from bacteria to be tested is fixed to a nylon or nitrocellulose filter and a probe made from the target gene is hybridized to the target DNA. To enable conditions to be established various information can be considered but the following material; is particularly useful. The equation: $Tm = 81.5°C - 16.6(\log10[Na+]) + 0.41 (5G+C) - 0.63$ (% formamide) $- (600/l)$ can be used to calculate the Tm of the probe provided Na+ concentration is in the range of 0.01M to 0.4M; G+C content is between 30% to 70%, and l is the length of the probe helps establish the conditions required. The equation can also be reversed to help determine the washing conditions to be used. The Tm of a double stranded DNA hybrid decreases by 1-1.5°C with every 1% decrease in homology (Bonner *et al.*, 1973; reduction in the rate of DNA re-association by sequence divergence. J. Mol. Biol. 81:123). In this way rough experimental conditions can be established where segments of DNA with very similar or very different DNA sequence can be isolated.

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9. I believe that those skilled in the art such as myself would be able to follow the methods as laid out in the patent application and common textbooks on DNA hybridization, many of which are standard in most laboratories around the world, to isolate genes that would be broadly considered to be within the same gene group as those described in the patent application, but have a significantly different sequence to those presented. Previously, I have used this method to obtain flagellin genes from two *Psuedomonas* strains (Winstanley, Morgan, Pickup, and Saunders 1994; Microbiology 140:2019). As such, DNA hybridization was a key tool to enable the isolation of similar groups of flagellin genes to those previously known. However, detailed analysis of these gene sequences has shown that for two of the genes described in this paper, regions of 1034bp (1st gene) can vary by 57% identity; and regions of 694 bp (2nd gene) can vary by 54% identity; to previously known genes and genes used to make the probe (Bellingham, Morgan, Saunders, Winstanley 2001 System, Appl. Microbiol. 24 157-165). This illustrates that genes with very different sequences can be isolated using DNA hybridization as a key tool.

AND I MAKE this declaration consciously believing the statements contained in this declaration to be true in every particular, and under penalty of perjury.

DECLARED at Warwick HRI 25th day of January 2005

J. A. W. Morgan